Investigational Agents for Prostate Cancer

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The past two years have marked an interesting and exciting time in the development of new therapies for advanced prostate cancer. Docetaxel’s approval for the treatment of castrate-resistant prostate cancer (CRPC) in 2004 was the first new therapy approved since the gonadotropin-releasing hormone agonists and antiandrogen therapies in the 1980s.

Docetaxel was previously the only modern chemotherapy agent to demonstrate an overall survival advantage in CRPC, and now we’ve had three new medical therapies recently approved in the past two years on the basis of prolonged overall survival: sipuleucel-T (Provenge), cabazitaxel (Jevtana) and abiraterone acetate (Zytiga).

Sipuleucel-T was approved in April 2010 for use in CRPC that is asymptomatic or minimally symptomatic. It is uniquely classified as an autologous cellular immunotherapy. After the collection of the patient’s peripheral blood mononuclear cells, they are delivered to a central manufacturing site and processed with recombinant fusion proteins, containing both prostate acid phosphatase and granulocyte-macrophage colony-stimulating factor elements. The product is then sent back to the patient and physician to infuse three times over a four-week period. Sipuleucel-T was initially tested in a phase 2 trial of 127 patients assessing time to progression as a primary endpoint, which was found to be insignificant, but a surprisingly significant overall survival difference of 25.9 versus 21.4 months compared with placebo was observed. A larger phase 3 trial then randomized 512 subjects with metastatic CRPC to sipuleucel-T versus placebo in a 2:1 design. Once again, overall survival of 25.8 months versus 21.7 months was noted in favor of sipuleucel-T. In addition, 64 percent of the patients on placebo received the immunotherapy on crossover. Toxicity centered mostly on chills, fever and headache, although few of these were found to be difficult to manage. The primary debate around the use of
this exciting new therapy has been its $93,000 price tag for a standard course and the fact that many of these patients are in the Medicare population.

Cabazitaxel was approved by the U.S. Food and Drug Administration in 2010 for the treatment of metastatic CRPC after failure of docetaxel chemotherapy. It is a noncross-resistant microtubule-targeted agent, and it was tested in an international phase 3 trial of 775 men, randomized to either cabazitaxel 25 mg/m² or mitoxantrone 12 mg/m² given intravenously every three weeks. Both treatment arms received prednisone. Overall survival of 15.1 versus 12.7 months in favor of cabazitaxel (p < 0.0001) was observed. Febrile neutropenia at 8 percent was the primary toxicity of concern in the cabazitaxel group, although diarrhea, including a grade 3 rate of 6 percent, was also noted.

Abiraterone acetate received approval in April 2011 for the treatment of CRPC patients who had received prior docetaxel. This oral inhibitor of CYP17, a lyase and a key driver of testosterone production, abiraterone acetate directly suppresses extragonadal testosterone production, resulting in testosterone levels near zero. Phase 2 trials revealed prostate-specific antigen (PSA) responses, reductions of more than 50 percent, ranging from 36 percent to 67 percent. Interestingly, patients who had previously been treated with ketoconazole showed little treatment responses and were excluded from the phase 3 trial.

An international, randomized phase 3 study of abiraterone acetate randomized patients to the investigational therapy plus prednisone versus best supportive care plus prednisone in a 2:1 fashion. Median overall survival for abiraterone acetate was 14.8 months compared with 10.9 months in the placebo arm (p < 0.001). In addition, an improvement in PSA progression of 10.2 months versus 6.6 months was noted, as well as a PSA response rate of 29 percent versus 6 percent, all favoring abiraterone acetate. Toxicities were mild and manageable, including fluid retention (31 percent), hypokalemia (17 percent) and hypertension (10 percent). Phase 3 studies in chemonaive patients are under way with accrual completed and results anticipated. MDV3100 is an oral androgen receptor signaling inhibitor (ARSI) in development for the treatment of early-stage and advanced prostate cancer. The novel mechanism of action is distinct from other hormonal therapies, including bicalutamide and abiraterone. MDV3100 competitively inhibits androgen binding to the receptor, inhibits movement of the receptor to the nucleus of prostate cancer cells and inhibits binding to DNA. The pivotal phase 3 AFFIRM trial completed enrollment in 2010 for advanced prostate cancer previously treated with docetaxel. In November 2011, a planned interim analysis showed that MDV3100 significantly improved survival compared with placebo. Specific results documented an 18.4 months versus 13.6 months median survival (hazard ratio 0.63) favoring MDV3100. The trial was thus stopped, and the placebo patients were allowed to receive MDV3100. Side effects were modest, and a favorable risk-benefit ratio for the new therapy was observed. The phase 3 PREVAIL trial is enrolling patients with advanced prostate cancer who have not received prior chemotherapy. Studies in earlier stages of this disease comparing MDV3100 with bicalutamide, as well as evaluating monotherapy, are now under way. Medivation is partnering with Astellas in a comprehensive drug development program for MDV3100.

Orteronel (TAK-700), a novel nonsteroidal lyase inhibitor, is also in development from Millennium Takeda. Its selectivity may be associated with less mineralocorticoid excess, potentially leading to an improved side-effect profile. Randomized phase 3 trials with TAK-700 are under way in advanced prostate cancer.

It is clear that we are closer to making advanced prostate cancer a chronic disease. With this abundance of new therapies, understanding the appropriate sequence of utilizing these agents will require well-conducted clinical trials.